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*Objective. In previous studies, cranial electrostimulation (CES) had positive effects on sleep in depressed patients and in patients with vascular dementia. The present study examined the effects of low-frequency CES on the rest-activity rhythm and cortisol levels of patients with probable Alzheimer's disease (AD). Method. It was hypothesised that a decreased level of cortisol would parallel a positive effect of low-frequency CES on nocturnal restlessness. Sixteen AD patients were randomly assigned to an experimental group (*n = *8) or a control group (*n = *8). The experimental group was treated with CES, whereas the control group received sham stimulation, for 30 minutes a day, during 6 weeks. The rest-activity rhythm was assessed by actigraphy. Cortisol was measured repeatedly in the saliva throughout the day by means of salivette tubes. Results. Low-frequency CES did not improve the rest-activity rhythm in AD patients. Moreover, both groups showed an increase instead of a decrease in the level of cortisol. Conclusions: These preliminary results suggest that low-frequency CES has no positive effect on the rest-activity rhythm in AD patients. An alternative research design with high-frequency CES in AD is discussed.*

Key Words: *Cranial Electrostimulation—Alzheimer's disease—rest-activity rhythm—salivary cortisol.*

Cranial electrostimulation (CES) is a noninvasive type of intervention in which mild electrical stimulation is applied to the head.[1] CES is aimed at lowering anxiety and depression in various withdrawal conditions.[1-7] The results of a meta-analysis of randomized controlled trials indicate that a reduction in anxiety appears to be the most consistent effect of CES.[8]

The effects of CES on sleep have been examined in only a few studies. Philip and coworkers[3] observed stability in sleep duration in depressed patients who were treated with CES, whereas a significant shortening of the sleep period was found in the placebo group. A sleep diary and a sleep questionnaire assessed quality of sleep. To our knowledge, CES was applied in only one study to demented elderly, that is, elderly with a vascular dementia.[9] Behavioral disorders and disturbances in sleep decreased after 2 weeks of treatment. However, also the sleep quality in the control group improved (sleep diary), possibly due to an increased level of daytime vigilance caused by the treatment-related interaction with the nurses.[9]

Hozumi et al.[9] suggested that CES might partly be mediated through the peripheral nervous system. A type of electrostimulation that is completely mediated by the peripheral nervous system is transcutaneous electrical nerve stimulation (TENS). Interestingly, TENS significantly improved the rest-activity rhythm in patients in both early and more advanced stages of Alzheimer's disease (AD).[10,11] The improvement in rest-activity rhythm indicated a stronger coupling between the rest-activity rhythm and supposedly stable Zeitgebers. In addition, nocturnal restlessness in the AD patients decreased. These findings suggest that TENS may stimulate the hypothalamic suprachiasmatic nucleus (SCN), the biological clock of the brain that is related to disturbances in circadian rest-activity rhythms in AD.[12,13]

Further support for a mutual mechanism underlying CES and TENS emerges from studies on the effects of both types of electrostimulation on various neurotransmitters. TENS might activate, for example, the hypothalamus through direct spino-hypothalamic pathways[14] but also indirectly

From the Departments of Clinical Neuropsychology (ES, J-BD, JS), Pharmacology (RB, FT), Medical Faculty (DK), Vrije Universiteit; and Netherlands Institute of Brain Research (EVS), Amsterdam, the Netherlands.

Address correspondence to Erik J. A. Scherder, PhD, Department of Clinical Neuropsychology, Vrije Universiteit, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands. E-mail: EJA.Scherder@psy.vu.nl.

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through the locus coeruleus (LC) and dorsal raphe nucleus (DRN).[15,16] These two brain stem areas—both affected in AD[17]—are the origin of the ascending noradrenergic and serotonergic neurotransmitter systems, respectively.[18,19] Therefore, both brain stem areas are "target" areas in our electrical stimulation studies. Interestingly, increased levels of noradrenaline and serotonin have also been observed after transcranial electrostimulation therapy in rats.[20] Transcranial electrostimulation therapy is synonymous with CES.

Although the neurons of the LC/noradrenergic system and the DRN/serotonergic system are capable of reacting to both low and high frequency stimulation,[21-24] it is noteworthy that different stimulation frequencies have a different effect on both systems. Low-frequency stimulation of, for example, 0.1 or 4 Hz preferably appeals to the LC/noradrenergic system, compared to the DRN/serotonergic system.[23] The neurons of the DRN/serotonergic system are most responsive to high frequency stimuli of, for example, 10, 20, and 100 Hz.[23,25-27]

Improvement in the rest-activity rhythm by activating the hypothalamus was the main goal of the present study. There are strong projections between the LC and the hypothalamus/SCN,[16] and results of various recent studies suggest that, through the LC/noradrenergic system, low-frequency electrical stimulation activates the hypothalamus.[23,28,29] Therefore, it was hypothesized in the present study that low-frequency CES could decrease disturbance in the sleep-wake rhythm in patients in a relatively early stage of AD.

The extent of sleeplessness might be reflected in the level of cortisol.[30-32] An increased level of cortisol, indicative of a hyperactive hypothalamic-pituitary-adrenal axis, was found to coincide with sleep disturbance. Therefore, the second hypothesis of the present study implied that an improvement in the rest-activity rhythm by CES would be reflected in a decrease in the level of cortisol.

METHOD

Participants

The local ethics committee gave approval for the study. The sample consisted of 16 participants and was drawn randomly from a larger sample of 500 elderly persons who lived in a residential home. The participants gave their informed consent to undergo a first global screening.

All participants met the NINCDS-ADRDA criteria for the clinical diagnosis of probable AD.[33] The clinical symptoms of dementia had been present for at least 6 months. Subjects were excluded from participation in this study if they had a history of psychiatric disorder, alcoholism, cerebral trauma, cerebrovascular disease, hydrocephalus, neoplasm, epilepsy, disturbances of consciousness, or focal brain disorders. None of the participants had a pacemaker. All patients met the criteria for early AD, that is, stage 5 of the Global Deterioration Scale.[34] Level of cognitive functioning was assessed by the 20-item version of the Mini-Mental State Examination (MMSE), with a maximum score of 30.[35] The level of education was quantified on a 5-point Likert-type scale: elementary school not finished = 1, elementary school finished = 2, lower secondary school = 3, higher secondary school = 4, higher vocational training for 18+/university = 5.

The 16 participants were randomly assigned to an experimental group (n = 8: 2 males, 6 females) or a control group (n = 8: 1 male, 7 females). The mean age of the participants of the experimental group (M = 86.75) did not differ significantly from the mean age of the control group (M = 87.88), $t(14) = 0.38$, *ns*. The mean MMSE score of the experimental group (M = 17.88) was not significantly different from the mean MMSE of the control group (M = 20.38) (Mann-Whitney *U*: $z = 1.37$, *ns*). There was no significant difference between the level of education of the experimental group (M = 3.25) and the control group (M = 3.00) (Mann-Whitney *U*: $z = 0.26$, *ns*).

Following the first global screening, the participants and their families were extensively informed about the aim and procedure of the investigation and gave their informed consent to continue the screening procedure. Before onset of the treatment procedure, a trial treatment was applied to both the experimental and the control group. No negative reactions of the participants were observed. The participants and their relatives were not aware of the group in which they participated, thus preventing a possible bias.

Material and Procedure

ASSESSMENT OF THE CIRCADIAN RHYTHMS

The rest-activity rhythm. The circadian rest-activity rhythm was assessed noninvasively by an actigraph

(Actiwatch, Cambridge Neurotechnology, Cambridge, UK). The actigraph has the size and shape of a watch, is worn on the dominant wrist, and registers acceleration-induced wrist movements. The actigraph quantifies accelerations due to motor activity of the arm and integrates these over 1-minute periods. The participants were asked to wear the actigraph 24 hours a day for 1 week. From the resulting rest-activity rhythms, 3 nonparametric variables were calculated36 using the Actiwatch Sleep Analysis 2001 software (Cambridge Neurotechnology, Cambridge, UK). First, the interdaily stability (IS) variable that quantifies the strength of coupling between the rest-activity rhythm and supposedly stable Zeitgebers (e.g., meals) was calculated. The second variable was the intradaily variability (IV), which quantifies the fragmentation of the rhythm, that is, the frequency and extent of transitions between rest and activity. The third variable was the relative amplitude (RA). The RA quantifies the difference between the main activity (day) and rest (night) periods.

Salivary cortisol measurement. There is ample evidence that salivary cortisol is a reliable reflection of cortisol concentrations in blood.[37,38] It represents cortisol that is not bound to plasma proteins and, therefore, reflects the biologically active free hormone concentration. Salivary cortisol samples were obtained by means of salivette tubes (Sarstedt, Rommelsdorf, Germany). The participants were asked to chew on a cotton-wool swab for about 1 minute, which is sufficient to collect enough material for analyses.[38] Sampling took place at 9 different points during 24 hours. Sampling started immediately after the moment of awakening (measurement 1), which was different for each person. One and 2 hours later, the 2nd and 3rd measurement took place. The 4th sample was at noon, followed by a 5th sample at 2:00 PM. The 6th sample was scheduled 3 hours before the expected time to sleep (which was different for each participant), the 7th sample 2 hours before that moment, followed by an 8th sample 1 hour before sleep onset. The final 9th measurement was acquired just before the participant went to sleep. All saliva sampling was conducted between 7:30 AM and 9:30 PM. In view of the individual variation in awakening and sleep onset, it should be noted that only 2 occasions of measurement were the same for each participant, that is, at noon and at 2:00 PM. We decided not to collect saliva during the night because awakening was expected to interfere with cortisol level and rhythms. After sampling, the saliva was stored at –20 °C. Because the duration of the study was 1.5 years and the participants were randomly assigned to both groups in parallel, season effects can be disregarded.

Cortisol analysis. Salivary cortisol was measured by a coated tube radioimmunoassay with the Orion Diagnostica SPECTRIA Cortisol Ria Test (Orion Corporation Orion Diagnostica, Espoo, Finland).

PROCEDURE

Treatment. CES was applied by the AlphaStim 100, which generates bipolar asymmetric rectangular waves, with a frequency of 0.5 Hz[39] and an intensity between 10 and 600 μA. The electrodes were clipped on to the earlobes. The investigator adjusted the current until the patient indicated feeling a tingling sensation and/or dizziness and then reduced the current to just below the reported threshold of sensation. If the patient experienced no sensation, the current was increased to a maximum level (600 μA). The experimental group was administered stimulation time for 30 minutes each day. Participants were treated for a period of 6 weeks, 5 days a week between 15.00 and 19.00 hours. Participants in the control group were treated in the same way as the experimental group, only no current was administered. The interpersonal communication during the treatment was identical for both the control and the experimental groups.

Moments of measurement. The actigraphy and cortisol measurements took place before the 6-weeks treatment period with (sham) CES (pre), after the 6-weeks treatment period (post), and again after a treatment-free period of 6 weeks (delayed).

Statistical Analyses

Actigraphy. Actigraphic variables were analyzed by multivariate analyses of variance (MANOVA) with group (treatment and control group) as an independent factor and time (3 levels—pretreatment: T1, posttreatment: T2, and after a treatment-free period: delayed: T3) as a repeated measurements factor. Even when no significant interactions between group and time were found, the explorative character of this pilot study justified that the data were submitted to 1 degree of freedom interaction *F* statistics. When interactions between group and time occurred concerning T1 and T2, T2

Table 1. Means, Standard Deviations, and Analyses of Variance of the Various Scales and Actigraphy

	Experimental Group						Control Group						ANOVA Pre-Post	Effect Size	
	Pre		Post		Del		Pre		Post		Del				
Actigraphy	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*(1, 14)	*P*	η^2
IS	.53	.10	.56	.08	.53	.20	.43	.20	.48	.19	.47	.19	.03	0.87	.01
IV	1.32	.25	1.40	.28	1.55	.33	1.31	.38	1.47	.38	1.43	.44	.34	0.57	.03
RA	.83	.11	.79	.11	.71	.14	.63	.23	.59	.20	.59	.21	.04	0.86	.01

IS = Interdaily Stability; IV = Intradaily Variability; RA = Relative Amplitude; Del = delayed.

and T3, and T1 and T3, paired within-group *t* tests would be performed. This appeared not to be the case in the present study (see the Results section). Effect sizes (eta squared [η^2]) were calculated, that is, small < .01, medium < .06, and large ≥ .14.

The Bonferroni correction was applied to the significance level of $P < 0.05$, resulting in a critical value of $P < 0.01$. The SPSS-PC program[40] was used to analyze the data.

Cortisol measurements. The (at most) 27 cortisol measures per person were obtained at irregular times between 8:00 AM and 10:00 PM, which makes a repeated measures analysis of variance inapplicable. Instead, a multilevel analysis[41] is more appropriate.

Multilevel modeling is a general technique for the analysis of clustered or correlated data, for example, pupils within schools, children within families, and repeated observations within a person. In general, the level-1 units (pupils or children) are to be differentiated from the level-2 units (schools or families). Although perhaps less obvious, in the context of repeated measurements the level-2 units represent the persons and the level-1 units the measurements. Standard repeated measures ANOVA and MANOVA are both special cases of the multilevel model. An advantage of the multilevel modeling is that missing data can be dealt with in a rather easy way (in our data set, we have 387 measurements from the maximum of 27 [9 samples at pre, post, and delayed measurement × 16 [2 groups × 8 participants in each group] = 432). A second advantage of multilevel modeling is that we can model the daily (24-h) cyclical pattern of the cortisol measures.[42]

It is well known that any periodic function can be fitted by a Fourier series, that is, a sum of sine and cosine waves.[43] To fit our data, 2 harmonics were needed, with period 24 h and 12 h, respectively. The effects of CES and time were modeled in the usual way by incorporating dummy variables for group (CES vs. placebo), time (post vs. pre and del (delay) vs. pre), and the Group × Time interaction to the model. The fixed part of the model can be symbolically written as

$$\text{Cortisol} = \text{Intercept} + \text{Group} + \text{Time} + \text{Group} \times \text{Time} + \text{Sin}\,\frac{2\pi t}{24} + \text{Cos}\,\frac{2\pi t}{24} + \text{Sin}\,\frac{4\pi t}{24} + \text{Cos}\,\frac{4\pi t}{24},$$

where *t* is the time in hours between 0 and 24 at which the measurement takes place.

To allow for variability between persons, a random model for the level-2 units has to be defined. Usually, some terms of the fixed part of the model are needed as random level-2 terms. For our data, random intercept terms and the sine and cosine terms of the first harmonic were needed. Finally, a random measurement term (represented by the level-1 intercept term) was added to complete the model.

Considering the paucity in studies in this field and conflicting results of some of the studies, two-tailed tests were used here. Multilevel analysis was performed with the MLwiN (version 1.10) software package.[44]

RESULTS

Effects of CES on the Rest-Activity Rhythm

Means and standard deviations are presented in Table 1. Repeated measures MANOVA did not reveal significant Group × Time interaction effects for IS, $F(2, 11) = 0.12$, $P = 0.89$; IV, $F(2, 11) = 1.79$, $P = 0.21$; and RA, $F(2, 11) = 0.56$, $P = .59$. One degree of freedom interaction *F* statistics did not show any significant difference between both groups after the treatment period (T1-T2).

Effects of CES on Salivary Cortisol

The fitted multilevel model (see Data Analyses in the Method section) for the mean curves is shown

in Figure 1, and the parameter estimates are given in Table 2 (interaction model). From these estimates, the 6 Group × Time mean curves are computed, evaluated at value 0 for the periodic function (see Table 3). As can be seen in Figure 1, the minimum cortisol level occurred at about 6:00 PM, whereas the projected maximum level (not shown in Figure 1) was reached at about 3:00 AM. The amplitude of the rhythm, that is, the difference between the minimum and the maximum, was 21.20 nmol/l. However, the results on amplitude and peak time should be considered with caution because the maximum cortisol level has been obtained by extrapolation from the fitted curves.

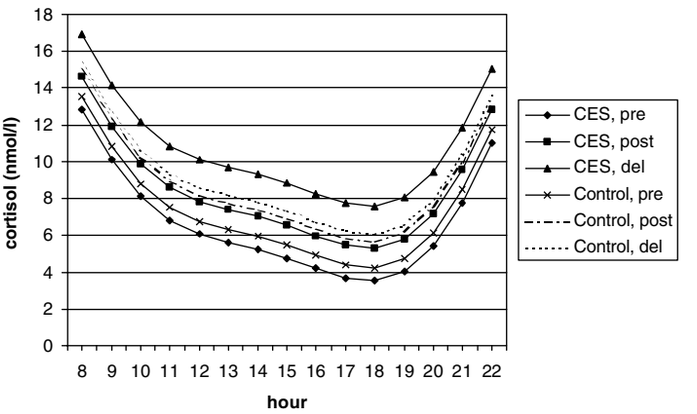

Figure 1. The fitted multilevel model for the mean values of saliva cortisol (nmol/l) of the experimental and control group between 8:00 AM and 10:00 PM. Pre = pretreatment; post = posttreatment, del = delayed (after treatment-free period); CES = cranial electrostimulation.

Data analyses further showed that there was no significant interaction effect between group and time, including Group × Post (T2) and Group × Del (T3) (likelihood ratio chi-squared = 3.70, $df = 2$, $P = 0.16$). The mean cortisol values as presented in Tables 2 and 3 clearly indicate that in both groups, the change in cortisol levels was in the unpredicted direction; that is, after CES (at T2) the cortisol level was increased, whereas we hypothesized a decrease in the experimental group only. Because the Group × Time interaction was not significant, the model was also fitted without interaction. The parameter estimates are shown in Table 2 (no interaction model). We tested in this model the main effects of time: likelihood ratio chi-squared = 20.47, $df = 2$, $P < 0.0001$ (post vs. pre: $z = 2.75$, $P = 0.006$; del vs. pre: $z = 4.57$, $P < .0001$).

DISCUSSION

The results suggest that low-frequency CES has no beneficial influence on the rest-activity rhythm and cortisol levels in AD patients. The mean scores on the actigraphy variables IS, IV, and RA hardly changed (Table 1). Furthermore, after both CES treatment and after placebo, cortisol levels were significantly increased (Table 2, Table 3, Figure 1). The level of cortisol further increased during the period without treatment.

In the present study, the lowest cortisol level occurred at 6:00 PM (Figure 1), not an unusual finding in AD.[45] However, in AD the cortisol level has been reported to remain at this level until midnight,[45] whereas in our patient group the cortisol level increased directly after 6:00 PM (Figure 1). Our patients were institutionalized, and after 6:00 PM the preparations for the night are already starting. For the residents, this is often a stressful event, possibly causing an increased cortisol response.[46]

The question arises whether a conclusion about the ineffectiveness of low-frequency CES in AD is appropriate, considering the small number of participants. However, a comparable number of participants were included in previous studies that did report beneficial effects of CES[47] and TENS[10,11] on the rest-activity rhythm. Because CES has never been applied to AD patients, effect sizes and, consequently, the number of participants could not be estimated before the start of the present study. In our opinion, by examining a new type of intervention that is very time-consuming and therefore costly, it is most important to perform a study of feasible sample size, calculate effect sizes, and evaluate the direction of the change in scores. The data show that in this group of patients, *clinically* relevant effects will not be obtained with this CES procedure. Therefore, in our opinion it is justified to discontinue the investigation of *low*-frequency CES as a treatment for circadian rhythm disturbances in AD.

Another important question is why low frequency CES was ineffective in AD. In 2 animal experimental studies and 1 human fMRI study with healthy participants, the activation of the hypothalamus was enhanced by low-frequency electroacupuncture and mediated by the LC/noradrenergic system.[23,28,29] However, in the present study, low-frequency CES was applied to AD patients with an extensive neuropathology, affecting more than 1 neurotransmitter system, for example, the serotonergic and the noradrenergic system.[48] One could argue that to obtain a more effective activation of the hypothalamus in AD, the LC/noradrenergic and DRN/serotonergic system might have to

Table 2. Parameter Estimates and Standard Errors (SE) of the Multilevel Two-Harmonics Models to Fit the Cortisol Level in the Experimental Group and the Control Group, at Baseline (pre), after a 6-Week Treatment Period (post), and after a 6-Week Treatment-Free Period (del)

	Interaction Model		No Interaction Model	
Fixed Effects	Parameter Estimate	*SE*	Parameter Estimate	*SE*
Intercept	12.56	1.68	12.19	1.65
Group (treatment versus control)	–0.71	1.20	–0.001	1.01
Time				
Post (vs. pre)	1.44	0.83	1.63	0.59
Del (vs. pre)	1.84	0.83	2.81	0.61
Group × Time				
Group × Post	0.34	1.17		
Group × Del	2.22	1.23		
Sin $\frac{2\pi t}{24}$	7.88	1.33	7.90	1.34
Cos $\frac{2\pi t}{24}$	6.23	1.77	6.28	1.77
Sin $\frac{4\pi t}{24}$	2.90	0.88	2.90	0.88
Cos $\frac{4\pi t}{24}$	0.44	0.49	0.48	0.49
Random Effects	Variance Component	*SE*	Variance Component	*SE*
Level 2				
Var(intercept)	22.83	8.88	22.93	8.92
Var(sin $\frac{2\pi t}{24}$)	11.94	5.53	12.00	5.56
Var(cos $\frac{2\pi t}{24}$)	27.27	11.32	27.23	11.32
Cov(intercept, sin $\frac{2\pi t}{24}$)	15.94	6.66	16.02	6.92
Cov(intercept, cos $\frac{2\pi t}{24}$)	22.67	9.45	22.53	9.44
Cov(sin $\frac{2\pi t}{24}$, cos $\frac{2\pi t}{24}$)	16.83	7.44	16.86	7.46
Level 1				
Var(intercept)	22.15	1.70	22.35	1.72
–2 log likelihood	2348.64		2352.34	

Research question is presented between bold lines.

be stimulated simultaneously to mimic neurophysiology as much as possible. Results from animal experimental studies indicate that the influence of the DRN/serotonergic system on the LC/noradrenergic system, which contains serotonin perikarya, is essential for the function of the latter system.[49] For example, the serotonergic system might exert an excitatory influence on the noradrenergic system, resulting in an increased release of serotonin in the LC[26] and a subsequent increased release of noradrenaline in the hypothalamus.[50] These latter findings imply that for an optimal functioning of the LC, the interaction between DRN and LC is a prerequisite.[49] Consequently, not only stimulation of the LC/noradrenergic system but also of the DRN/serotonergic system should be included in the treatment. In the TENS studies, in which the circadian rest-activity rhythm of AD patients improved,[10,11] the selective sensitivity of the serotonergic and noradrenergic neurotransmitter systems for high- and low-frequency stimulation, respectively, could be met by using the BURST-TENS mode.[51] In the BURST-TENS mode, high- and low-frequency stimulation are combined in 1 treatment; that is, a frequency of 160 Hz is applied to the patients in 2 bursts per second (2 Hz), that is, 2 blocks of trains of impulses.

In contrast to BURST-TENS, CES can be applied only in a low- or high-frequency mode: 0.5 and 100 Hz, respectively. As noted in the introduction, the neurons of the DRN/serotonergic system preferably respond to *high* frequency stimulation, for example, 10 and 100 Hz.[26,27] It should be noted, however, that the LC/noradrenergic neurons are well able

Table 3. Mean Cortisol Levels Computed at Value 0 for the Periodic Function before Treatment (T1), after Treatment (T2), and after a Treatment-Free Period (T3)

	Cortisol Levels		
	Pretreatment (T1)	Posttreatment (T2)	Delayed (T3)
Treatment group	11.85	13.62	15.91
Control group	12.56	14.00	14.40

Treatment is either cranial electrostimulation (treatment group) or placebo (control group).

to react to high-frequency stimulation of, for example, 100 Hz.[23] Support for high-frequency CES as a possible more effective treatment strategy in AD emerges from studies with transcranial magnetic stimulation (TCMS). Kimbrell and coworkers[52] observed that the effectiveness of TCMS on depression appeared to be dependent on the level of baseline glucose metabolism. A frequency of 20 Hz showed a higher antidepressant effect in patients with a baseline cerebral glucose hypometabolism, whereas a frequency of 1 Hz was most effective in patients with a baseline cerebral glucose hypermetabolism. It is known that the global level of brain glucose metabolism shows a significant decrement in AD compared to nondemented elderly persons.[53] These authors argued that in AD, neuropathological changes such as atrophy lower the brain metabolism. Conversely, a low glucose metabolism is found to increase the risk for dementia.[54]

In sum, the results of studies that indicate that both the DRN/serotonergic system as well as the LC/noradrenergic system are able to respond to high-frequency stimulation, together with the effectiveness of high-frequency TCMS in patients with cerebral glucose hypometabolism, justify a next study on the hypothesis that, instead of low-frequency CES, high-frequency CES improves the rest-activity rhythm in AD patients.

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